The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

EMEA/MRL/461/98-FINAL
July 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

JOSAMYCIN (pigs)

SUMMARY REPORT

1. Josamycin is a 16-membered ring macrolide antibiotic identical to leucomycin A_3 and obtained by fermentation of *Streptomyces narbonensis*. Josamycin is effective *in vitro* against mycoplasma, Gram-positive cocci (*Staphylococcus spp.*, *Streptococcus spp.*, *Diplococcus spp.*). The standard potency is 1000 IU/mg. In veterinary medicine, it is administred in chicken for the prevention and the treatment of chronic respiratory diseases, sinusitis, synovitis and arthritis caused by mycoplasma and Gram-positive germs by oral route via drinking water or by premix feed at a daily recommended dosage of 9 to 18 mg/kg bw per day for 3 to 5 days.

   A provisional microbiological ADI of a 0.002 mg/kg bw based on the MIC of the most sensitive strain *Bacteroides fragilis* had been previously established.

   Currently, josamycin is included in Annex III of Council regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Josamycin	Josamycin	Poultry	200 µg/kg 200 µg/kg 200 µg/kg 400 µg/kg 200 µg/kg	Muscle Fat Liver Kidney Eggs	Provisional MRLs expire on 1.7.2000

   Additional residue data were provided to include pigs into the current entry. In pigs, josamycin is recommended for the prevention and the treatment of chronic respiratory diseases at the recommended dose of 9 to 18 mg/kg bw per day up to 14 days.

2. After administrations of josamycin (18 mg/kg bw/day for 5 days) to 5 pigs, the residue levels in all edible tissues (one animal per sampling time) were below the limit of quantification of the analytical method used (microbiological method with a limit of quantification of 100 µg/kg for liver, muscle and fat, and 200 µg/kg for kidneys) at five days after the end of the treatment.

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3. In a depletion study, four groups of 4 pigs received via drinking water oral doses of 18 mg josamycin kg/bw per day for 14 consecutive days. Animals were slaughtered at 1, 3, 7 and 14 days after the end of the treatment. The concentrations of josamycin in edible tissues were determined both by a microbiological assay method (limit of quantification 100 µg/kg) and by an HPLC method (limits of quantification and detection 100 and 50 µg/kg, respectively). One day after the end of the treatment significant amounts of microbiologically active residues were measured in all edible tissues, they were in the magnitude of 3000 µg/kg for muscle, fat and skin, 200 µg/kg in kidney and in the range of non detected to 130 µg/kg for liver. Two days after the end of the treatment, large amounts of microbiologically active compounds were still measured in fat (4100 µg/kg), skin (approximately 780 µg/kg) and kidney (from less than 100 to 1660 µg/kg). In muscle the concentrations were much lower, the highest value being 190 µg/kg. For later sampling times, the concentrations of microbiologically active compounds were either below the limit of quantification (100 µg/kg) or not detected.

   No significant amounts of josamycin could be measured by the HPLC method. The concentrations were in the region of the limits of quantification and detection.

4. As josamycin represents only a low percentage of the total microbiologically active substances in edible tissues, the parent compound could not be selected as the marker residue for edible tissues.

5. Although an HPLC analytical method has been validated for determining residues of josamycin in edible tissues of pigs, it was considered not being suitable because the parent compound represented a negligible percentage of the microbiologically active compounds. A microbiological method was provided, however, due to the general lack of specificity of microbiological methods, this is not considered to be a validated routine analytical method in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community.

Conclusions and recommendation

Having considered that:

- a provisional microbiological ADI of 0.002 mg/kg bw (i.e. 120 µg/person) for josamycin had previously been established,
- the parent compound could not be retained as marker residue as it is metabolised to microbiologically active compounds,
- additional studies must be carried out to determine the choice and the ratio of the marker residue in edible tissues of pigs,
- there is a microbiological analytical method for the determination of active residues;

the Committee recommends the inclusion of josamycin for pigs in Annex III of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Josamycin	Sum of the microbiologically active metabolites, expressed as josamycin	Porcine	200 µg/kg 200 µg/kg 200 µg/kg 400 µg/kg	Muscle Skin + fat Liver Kidney	Provisional MRLs expire on 1.7.2002

Based on these MRLs values, the daily intake will represent 85% of the microbiological ADI.

Before the Committee can consider the inclusion of josamycin in Annex I of Council Regulation (EEC) No. 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The applicant should propose a residue marker for all edible tissues (muscle, liver, kidney, skin+fat) and establish the ratio of the marker residue towards the microbiological active residues in pigs.

2. The applicant should provide a suitable analytical physicochemical method for the determination of residues in edible tissues of pigs. This method should be validated according the recommendations of Volume VI of the Rules Governing Medicinal Products in the European Community and described according to an internationally recognised standard layout (e.g. ISO 78/2).